The upper airway volume effects produced by Hyrax, Hybrid-Hyrax, and Keles keyless expanders: a single-centre randomized controlled trial

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Abstract: OBJECTIVE To assess upper airway volume changes after rapid maxillary expansion (RME) with three different expanders. TRIAL DESIGN Three-arm parallel randomized clinical trial. METHODS Sixty-six patients, 10-16 years old, in permanent dentition, with maxillary transverse deficiency were recruited and assigned with block randomization (1:1:1 ratio) and allocation concealment to three groups of 22 patients each (Hyrax, Hybrid-Hyrax, and Keles keyless expander). The primary outcome (overall upper airway volume change) and secondary outcomes (volume changes in the nasal cavity, nasopharynx, oropharynx, and hypopharynx) were blindly assessed on the initial (T0) and final (T1, 6 months at appliance removal) cone beam computed tomography. Differences across groups were assessed with crude or adjusted for confounders (gender, age, growth stage, skeletal pattern, baseline airway volume, and amount of expansion) linear regression models. RESULTS Fifty-one patients were analysed (19, 19, and 13 in the Hyrax, Hybrid-Hyrax, and Keles groups). Maxillary expansion resulted in considerable increases in total airway volume in the Hybrid-Hyrax group (+5902.1 mm3) and less in the Hyrax group (+2537.9 mm3) or the Keles group (+3001.4 mm3). However, treatment-induced changes for the primary and all secondary outcomes were of small magnitude and no significant difference was seen among the three expanderes in the total airway volume in either crude or adjusted analyses ($P > 0.05$ in all instances). Finally, among pre-peak patients (CVM 1-3), the Hybrid-Hyrax expander was associated with significantly greater increases in total airway volume compared to the Hyrax expander ($P = 0.02$). CONCLUSIONS RME resulted in relatively small increases in total upper airway volume and its separate compartments, with mostly no statistically significant differences across the Hyrax, Hybrid-Hyrax, and Keles groups. LIMITATIONS Significantly greater attrition was found in the Keles group due to appliance failure. The current trial might possibly be under-powered to detect differences between groups, if such exist. HARMS Keles expanders blocked during activations and required substitution for completion of treatment. PROTOCOL The protocol was not published before trial commencement. REGISTRATION Australian and New Zealand Clinical Trial Registry (ACTRN12617001136392).

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The upper airway volume effects produced by Hyrax, Hybrid-Hyrax and Keles keyless expanders: a single-centre randomised controlled trial.

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Summary

Objective: To assess upper airway volume changes after rapid maxillary expansion (RME) with three different expanders.

Trial design: 3-arm parallel randomised clinical trial.

Methods: Sixty-six patients 10-16 years old, in permanent dentition, with maxillary transverse deficiency recruited and assigned with block-randomisation (1:1:1 ratio) and allocation concealment to three groups of 22 patients each (Hyrax, Hybrid-Hyrax, Keles keyless expander). The primary outcome (overall upper airway volume change) and secondary outcomes (volume changes in the nasal cavity, nasopharynx, oropharynx, hypopharynx) were blindly assessed on the initial (T0) and final (T1, 6 months at appliance removal) Cone Beam Computed Tomography (CBCTs). Differences across-groups were assessed with crude or adjusted for confounders (gender, age, growth stage, skeletal pattern, baseline airway volume, and amount of expansion) linear regression models.

Results: Fifty-one patients were analysed (19, 19, and 13 in the Hyrax, Hybrid-Hyrax, and Keles groups). Maxillary expansion resulted in statistically significant increases in total airway volume only in the Hybrid-Hyrax group (+5902.1 mm^3; P<0.001), but not in the Hyrax group (+2537.9 mm^3; P=0.11) or the Keles group (+3001.4 mm^3; P=0.34). However, treatment-induced changes were of small magnitude and no significant difference was seen in the total airway volume in either crude or adjusted analyses (P>0.05 in all instances). Similarly, no statistically significant differences in the treatment-induced changes for any of the secondary outcomes were found across groups.

Conclusions: RME resulted in relative small increases in total upper airway volume and its separate compartments, with no statistically significant difference across the Hyrax, Hybrid-Hyrax, and Keles groups.

Limitations: Significantly greater attrition in the Keles group due to appliance failure. The current trial might possibly be under-powered to detect differences between groups, if such exist.

Harms: Keles expanders blocked during activations and required substitution for completion of treatment.

Protocol: The protocol was not published before trial commencement.

Registration: Australian and New Zealand Clinical Trial Registry (ACTRN12617001136392).

Introduction

Rationale

Rapid maxillary expansion (RME) appliances are often used to treat transverse deficiencies in the maxilla since their introduction in the 1860s (1) with both skeletal and dentoalvoelar effects (2). Two of the most commonly used RME designs include the Hyrax and Haas expanders, which however are also associated with undesirable tooth movement and tipping due to the way forces are applied (3). RME appliance activation with an external key may be a challenge as patients, parents or guardians may find it difficult to use and require external help. Furthermore, the key may potentially be an aspiration hazard (4) as well cause lacerations to the palatal mucosa, if used incorrectly. As a result, the development of an effective keyless expander could be beneficial and patient friendly regarding cooperation with the activation scheme. In the last decade attempts have been made to incorporate skeletal anchorage devices to the RME appliance, in an effort to minimize its dentoalveolar and increase its skeletal effects (5). Nonetheless, the increased invasiveness of the procedure, possibility of the loss of the anchorage devices, and the risk of infection (6-8) have restricted the widespread use of skeletally-anchored RME.

The impact of orthodontic treatment on the airways has received increased interest in the latter years with studies showing that, in addition to its orthodontic effects, RME can have a positive effect on airway dimensions and breathing function (9). The mechanism of action is believed to derive from the increases of nasal width with subsequent enlargement in upper airway volume and decrease in nasal resistance (9, 10). A significant increase in nasal airflow and reduction in airway resistance were found with Hybrid-Hyrax expanders using rhinomanometry immediately after expansion (11). These beneficial effects of RME have been highlighted as a therapeutic possibility in children diagnosed with obstructive sleep apnoea, who showed reduction in the Apnoea-Hypopnea Index (AHI) after RME treatment (12).

The upper airway has been traditionally measured using two-dimensional imaging (lateral cephalometric radiographs); however, there are considerable limitations of measuring a three-dimensional volume from a two-dimensional image (13). Advances in three-dimensional imaging (magnetic resonance imaging, computed tomography, and Cone Beam Computed Tomography [CBCT]) have allowed better visualisation and reliable analysis of the airway volumes (13-15). Several studies have investigated airway changes after RME using CBCT (16-20). Cordasco et al 2012 evaluated retrospectively a sample of eight children receiving maxillary expansion with a conventional tooth-borne expander while the area of interest and subsequent linear and volumetric measurements

were performed and confined to the nasal cavity only (16). Gorgulu et al 2011, included similarly one group of 15 patients aged 12-16 years, all of whom received a bonded tooth-borne expander with acrylic coverage and airway measurements were basically focused to the nasal cavity (17). Another study investigated the changes induced in the nasal airway volume by a tooth anchored acrylic cap splint appliance with a hyrax screw in 10 Class I and 14 Class II children of 14.5 years of age (18). Even though Smith et al 2012 investigated treatment changes due to RME (banded in 1st permanent premolar and molars) in all upper airway compartments, the use of only one appliance design does not permit comparisons with any other type of expanders and the retrospectivity of the study comes with the relevant biases in study design (19). With the introduction of skeletal anchorage, purely bone-bone appliances such as the Dresden Distractor have been used in conjunction to Surgically Assisted rapid Maxillary Expansion (SARME) in adult patients (20). Further to this, comparison of upper airway changes after RME with a Hyrax expander and a purely bone-borne expander was performed through Acoustic Rhinometry in growing individuals (21) while a hybrid appliance anchored to the 1st permanent premolars and molars and 4 miniscrews (1.8x7mm) was assessed in 14 adults using CBCTs (22). Evidence from the literature depicts that the available studies render issues relevant to study design such as randomisation, allocation of treatment, blinding of the assessors during measurements, inclusion of only one RME appliance, retrospective evaluation of patient record and sample size to mention few.

Objectives

The aim of this study was to assess the short-term changes in upper airway volume after RME with conventional tooth-borne (Hyrax), tooth-bone-borne (Hybrid-Hyrax), and the Keles keyless expander via CBCT.

Subjects and methods

Trial design and any changes after trial commencement.

This was a single-centre double-blind (outcome assessor and data analyst) parallel randomised controlled trial with a 1:1:1 allocation ratio.

Participants, eligibility criteria, and settings

The sample consisted of 66 healthy 10-16 year-old patients recruited from the orthodontic waiting list at Sydney Dental Hospital by the authors (G.C.C, S.M and S.H) from January 2017 to July 2017. The following inclusion criteria were applied: unilateral or bilateral posterior crossbite; maxillary transverse deficiency of >5mm as measured from the cusp of the upper first permanent molars to the lower first permanent molar central groove; erupted first permanent molars and premolars; adequate oral hygiene; no history of previous orthodontic treatment and no history of craniofacial defects, syndromes or surgery. Consent was obtained from the patients (and the parents of patients were adolescents before recruitment). Ethic approval was granted prospectively by the Sydney Local Health District RPAH Zone (X17-0075).

Intervention

Prior to orthodontic intervention, full records were taken for each patient constituting of study models, extra-oral photos, and intra-oral photos. Each patient was then randomised to a Hyrax, Keles or Hybrid-Hyrax RME appliance (Figure 1). At the first appointment, patients were informed about their treatment allocation, received their baseline CBCT (T0) and separators were placed between the contact points of first premolars and molars. Approximately a week later, molar/premolar bands were fitted and alginate impressions taken for expander fabrication. Patients in the Hyrax and Keles groups received a traditional Hyrax (Hyrax, Dentaurum, Ispringen, Germany) and Keles keyless expander (Keles, Istanbul, Turkey) soldered to bands on the first premolars and molars respectively. In patients allocated to the Hybrid-Hyrax group, 1.0ml Lignocaine-1:80,000 adrenaline was administered as a local anaesthetic infiltration in the anterior palatal area. A sterile gauze soaked in chlorhexidine was used to disinfect the palate in the area of insertion. Following this, predrilling was performed using a PSM Medical Solutions (Tuttlingen, Germany) drilling bur adapted to a contra-angle handpiece and rotated by hand to a depth of 7mm at a 90-degree angle to the palate at approximately the area of the third palatal rugae. Two Benefit miniscrews of length 9mm and 2mm width (PSM Medical Solutions, Tuttlingen, Germany) were placed bilateral to the midpalatal suture. Bands were fitted on the first permanent molars only and alginate impressions were taken using impression copings. Patients were instructed to use chlorhexidine mouthwash twice a day for one week, with gentle brushing of the miniscrews.

All appliances were inserted approximately 2 weeks after the impression appointment, with bands cemented using multi-cure Glass ionomer cement (3M Unitek, Maplewood, Minnesota). Patients were instructed to turn the expander twice a day (0.5mm) and to return for weekly reviews until palatal cusps of the upper first molars were in contact with the buccal cusps of the lower first molars. The expander was then locked and the patient instructed to return in 6 months unless there were any breakages. At 6 months, the appliances were removed and full records were taken including a second CBCT (T1). Treatment was provided by three providers (G.C.C., S.M. and S.H.).

CBCT images were taken using a NewTom 5G (Cone Beam 3D Imaging, Verona, Italy) imaging system at 110kV, 20mAs, 18x16cm, 0.3mm voxel size and 3.6 seconds per section with patients in a supine position. Head position was controlled by manually positioning the patient so that the Frankfort horizontal plane was perpendicular to the floor and patients instructed to stay still during the scan. For image acquisition and throughout the scanning process, patients were instructed after expiration to be in centric occlusion with the lips and tongue in resting position and not to swallow. Patients did not receive any orthodontic treatment during the study period; however, all additional to the constricted maxilla problems were addressed after completion of the present study.

Outcomes (Primary and Secondary) and any changes after trial commencement

The main outcome was the treatment-induced (T1-T0) changes in the overall airway dimension as measured on CBCT after expander use. The secondary outcomes included changes in the separate compartments of the airway: nasal cavity, nasopharynx and oropharynx between devices. A sensitivity analysis was also run by calculating changes in the overall ‘functional’ airway volume – the total airway without including the sinus volumes. Airway changes were assessed against factors such as baseline airway, gender, age, Cervical Vertebrae Maturation (CVM) stage, expansion width calculated by the days of expansion from the patients’ calendars, anteroposterior (SNA, SNB, ANB, Wits, convexity), vertical (mandibular plane angle SN-MP) and linear depth (SN, Co-A, Co-Gn) of the craniofacial morphology.

The reconstructed CBCT datasets were imported into the Dolphin 3D software (Dolphin Imaging, Chatsworth California, USA) as Digital Imaging and Communications in Medicine (DICOM) files. The files were then provided with a number by a third party uninvolved with the study so that the assessor (G.C.C.) was blinded to the patient and time points while performing the measurements.

All images were orientated prior to landmark identification. The sagittal plane was orientated in the Frankfort horizontal plane, with the coronal and axial plane orientated to the skeletal midline using the crista galli, anterior nasal spine, nasal bone and orbits as reference points (Figure 2). The 3-dimensional (3D) landmarks were based on landmarks used in previous studies for measurement of the 3D airways for the nasal cavity, nasopharynx and oropharynx (19, 23-25). The definitions for the airway boundaries are described in Table 1. In the Dolphin software, the boundaries of the nasal cavity, nasopharynx, oropharynx and hypopharynx were first located on the mid sagittal position in the coronal view (Figure 3, marked A, B, C, D respectively). The sinuses were outlined on coronal view at the section of the furcation of the maxillary first molar (Figure 3, marked E). Seed points were then placed in all air cavities within the boundaries. This included all sinuses and ethmoid air cells within the total airway boundaries. The images were cross checked in all three planes of place (sagittal, coronal and axial) and new seed points placed when required to ensure that all air cavities were included. The sensitivity threshold was kept to the maximum possible for each patient without detecting space outside the airway. Individual sensitivity thresholding was achieved for each sample by manually adjusting the threshold until the maximum threshold setting could be used without detecting space outside the anatomical limits of the airway. A starting threshold setting of 40 was used and this was changed incrementally until the highest threshold was reached. This was defined as when the 3D reconstruction of the airway demonstrated the correct airway morphology with no reconstruction of the space around the head. A threshold range between 50-70 was used for all scans (26, 27).

Error measurement

To examine measurement reliability and agreement, 25% of the sample was randomly selected and remeasured after 4 weeks. This involved reorientation of all images and reselection of the sensitivity threshold value for segmentation. The concordance correlation coefficient (28) and Bland-Altman method (29) were used to test intra-examiner reliability and agreement.

Sample size calculations

Sample size calculations were based on the ability to detect a clinically relevant difference of a 20% increase in airway volume, $\alpha = 0.05$ and a power of 80% in a 2-sided paired t-test. A mean of 23950mm^3 and standard deviation of 6431mm^3 data from a previous study using similar airway volume parameters

were used (19). This resulted in a sample size required of 15 patients per group. Twenty-two patients per group were chosen to be the final sample size to accommodate for dropouts and any possible image quality DICOM dataset issues that would have compromised the reliability of measurements.

Interim analyses and stopping guidelines

Predetermined factors for terminating and/or modifying treatment for patient safety reasons were the following: unresponsive tissues to expansion such as excessive buccal tipping with mobility of anchor teeth accompanied with lack of midline diastema after 1 week of expansion, appliance breakage, miniscrew infection and complete failure.

Randomisation (random number generation, allocation concealment, implementation)

Randomisation was accomplished using the "RANDBETWEEN" command in Excel 2016 software (Microsoft, Washington) to randomize patients into the three groups as blocks of 22 patients each. Allocation concealment was performed by a staff member at the Sydney Dental Hospital not directly involved with the trial. Separate sealed and opaque envelopes with each patient's allocation were held in a central location in the department until the day of treatment.

Blinding

The patient and operators could not be blinded to the intervention groups during treatment. Each CBCT dataset was given a coded ID number, with the de-identified coding list kept by staff not involved in the measurements and was released during dataset preparation. The datasets were provided with codes on the expander type (expander 1, 2, and 3) and time-points (time-point a and b) for blinded statistical analysis and the code was broken after supplying the results of the statistical analysis.

Statistical Analysis (primary and secondary outcomes, subgroup analyses)

Initially, descriptive statistics were calculated including absolute/relative frequencies (for categorical outcomes) or means and Standard Deviations (SDs) (for continuous outcomes). Afterwards, crude differences across experimental groups were assessed with one way analysis of variance and Fisher's exact test. Explorative linear regression models were constructed to assess the possible influence of patient age, gender, Cervical Vertebrae Maturation (CVM) stage, baseline cephalometrics of skeletal

pattern, pre-expansion airway volume, and expansion width on the treatment-related T1-T0 change in total airway volume. Finally, the effect of expander type on total airway volume at T1 with volume at T0 as covariate was assessed with either crude analysis or adjusting for any confounders. Interactions of confounders with expansion group were tried and dropped if not statistically significant (P>0.05). Significant interactions were further explored with stratified analyses. All analyses were run in Stata SE 13.0 (StataCorp, College Station, TX) with significance level set at a two-sided 5% and the dataset openly provided through Zenodo (30).

Results

Participant flow and recruitment

The patient flow in this study is demonstrated by the CONSORT flow diagram in Figure 4. All 66 patients who were deemed eligible for treatment were randomised in a 1:1:1 ratio to Hyrax, Hybrid-Hyrax or Keles expander. Patient recruitment started January 2017 and was completed in July 2017.

Numbers analysed for primary outcome and subgroup analysis. Baseline data

In the Keles group, 8 patients were excluded from the study and were further treated with a Hyrax expander. This was deemed necessary as it was found that their Keles keyless expanders suffered from structural defects related to blocking of the expander not permitting further activations, which made it clinically unsatisfactory to continue their use. It was decided that it would be unethical to continue. The expanders were replaced and these cases were excluded from the analysis. Additionally, 2 DICOM datasets form the Hyrax group and 3 from the Hybrid-Hyrax group were not of appropriate quality for performing upper airway measurements, due to patient movement during image acquisition, making further analysis not feasible. This resulted in a total of 51 remaining patients (19, Hyrax, 19 Hybrid-Hyrax, 13 Keles expander) that had CBCT images analysed for both time points, leaving a total of 102 datasets. Baseline data characteristics of the analysed patients show no significant differences between the three groups for all tested parameters (Table 2).

Measurement error

The concordance correlation coefficient was 1.00 (95% CI: 1.00-1.00) and the average differences of the repeated measurements was -52.39 mm^3 (95% limits of agreement -1029.29 to 924.51 mm^3; Bradley-Blackwood P=0.81), indicating excellent intra-examiner reliability and agreement.

Primary outcome

Table 3 shows the volumetric changes between T0-T1 within and among the Hyrax, Hybrid-Hyrax, and Keles expander groups. The total airway volume showed the greater increase after treatment in the Hybrid-Hyrax group (5902.1±5992.9mm^3; +8.3% from T0), followed by the Keles group (3001.4±10909.9 mm^3;+4.5% from T0), and the Hyrax group (2537.9±6603.7 mm^3; +3.8% from T0) with no statistically significant differences across the three RME groups for the total airway.

Secondary outcome

Similarly, no significant differences were seen between the groups for the total airway volume without including the sinuses (P=0.26). On average, more pronounced changes in all airway compartments were most of the time seen for the Hybrid-Hyrax group or the Keles group compared to the Hyrax group (Table 3). However, no significant difference was seen for any of the airway compartments across the three groups with the sole exception of nasopharynx exhibiting greater changes in the Keles group (P=0.04).

Exploring potential confounders across the whole sample, baseline airway volume at T0 was significantly associated in an inverse manner with the amount of treatment-induced (T1-T0) increases seen (P=0.02), while patient age, CVM stage, anteroposterior (SNA, SNB, ANB, Wits, NA-A-Pog), vertical (SN-ML) and linear (cranial base-SN, relative maxillary Co-A and mandibular Co-Gn lengths) cephalometric variables were also investigated as potential confounders (Supplementary Table 1).

Controlling with adjusted analyses for most confounders on the effects of the different expanders (Supplementary Table 2) showed that no significant difference was seen between the three expanders. However, a significant interaction term of the patients' CVM stage with the expander groups was found, which was further assessed by stratified analysis (Supplementary Table 3). This indicated that among pre-peak patients (CVM 1-3), the Hybrid-Hyrax expander was associated with significantly greater increases in total airway volume compared to the conventional Hyrax expander (P=0.02).

Harms

Minor discomfort and infection were associated in some patients due to miniscrews placement; however, this resolved after using chlorhexidine mouthwash and reinforcement of correct oral hygiene protocols. The Keles expander showed issues related to the activation rod, which became immobile and rendered further expansion inevitable. Patients whose Keles appliances exhibited the above issues had their devices substituted with Hyrax expanders for completion of treatment. Additionally, due to tipping of the anchor teeth in the Keles expander group, which was noted clinically during the weekly follow-ups of active treatment, activation was performed until posterior crossbite correction without attempting overcorrection (Table 2, amount of expansion).

Discussion

In this double-blinded randomised clinical trial CBCT data were used to evaluate the volumetric compartmental changes of the airway using two tooth-borne and one tooth-bone-borne expander. RME expansion treatment has been demonstrated to have a positive effect in airway change (19). The development of new expanders supported by TADs may have increased benefits on upper airway change as increased nasal flow rates and reduced resistance using tooth-bone-borne expanders was found when compared to tooth-borne expanders (4, 11). To the author's knowledge, no RCT using CBCT has been conducted to assess the volumetric changes between tooth-bone-borne and tooth-borne expanders. Therefore, the purpose of this study was to investigate and compare the effect of different types of expanders on the upper airway volume.

The use of three-dimensional volumetric data in this study has allowed us to overcome the limitations of analyses on two-dimensional lateral cephalograms. A number of studies have investigated the effects of rapid maxillary expansion on nasal cavity width, nasal resistance and airflow and have found increases in favourable results (31, 32). Nonetheless, anatomic changes were assessed in postero-anterior radiographs, which is a questionable method regarding its specificity in measuring a 3D entity such as the nasal cavity and the rest of the upper airway volume (13). A systematic review and meta-analysis on volumetric upper airway changes with tooth-borne RME reported an increase of 1218.3mm^3 in the total upper airway immediately post-expansion and in the nasal cavity. Nevertheless, many studies reported on miniscule clinically irrelevant changes from baseline, while the overall quality of evidence was low due to study design, lack of controls and inconsistency of boundaries set for the

measurements amongst researchers (33). Especially the latter issue makes comparison between articles difficult, with as many as six different definitions published for just the superior anatomical boundary of the nasopharynx showing lack of consensus in the literature (34).

Airway changes after RME using a Hyrax expander have also been investigated by other researchers (19), who have reported statistically significant increases in the volume of the nasal cavity and the nasopharynx (19). This differs from the findings of the present study and may be due to the younger cohort group as well as the short duration (3 months) before obtaining the post-treatment scan. In another retrospective study, both tooth-borne Hyrax and a purely skeletally anchored expander used in patients of similar age to the ones recruited in the present study resulted in significant changes in the nasal cavity and nasopharyngeal volumes (35). Even though their bone-bone expander created greater effects, these did not reach statistical significance, a finding which is in agreement to our comparisons between the three expanders. This could be due to the considerably variable response to RME across patients, which indicates that not all patients treated with RME might experience the same increase in airway volumes. However, both studies showed significant changes induced with the Hyrax in the nasal cavity and nasopharynx, which differs to our results on the Hyrax group. This could possibly be attributed to inter-individual patient anatomic factors and appliance construction characteristics. When the effects of palate depth, modified arm shape and anchor screw on RME expansion were tested with finite element analyses (FEA), it was reported that deep palate exhibited smallest RME effects, smallest midpalatal suture expansion and greatest arm strain. Additionally, arms of larger diameter, with diagonal connections, straight and short create more efficient maxillary expansion and are necessary even in the presence of skeletally anchored expanders (36).

In the present study, a tendency towards greater changes was found in the Hybrid-Hyrax group. FEA has been extensively used to assess stress distribution in various RME appliances. Superimposition of FEA models simulated to real expansion data derived from Hybrid-Hyrax CBCTs showed expander arm deformations and enormous stresses around miniscrews. Stresses were mainly concentrated around the Le Fort I plane and were greater in the infrazygomatic crest and the pterygomaxillary complex while there was lack of stresses around the molar anchor teeth (37). Similarly, RME anchored on micro-implants placed in various areas of the palate showed stress concentrations around the implants whereas stresses were still present on teeth even when surgically assisted RME was simulated in conjunction with the tooth-borne expanders (38). Comparison of the stresses

generated on the craniofacial structures by tooth-anchored and implant-supported RME showed that the former generated greater stresses on teeth and the later to the midpalatal and circumaxillary sutures (39). Based on the above literature, the tendency of the Hybrid-Hyrax to perform better in the nasal cavity and the total airway in our study could be attributed to the palatal implants, which most probably withstand the stresses developed during expander activation, and not to the different maturation levels of the midpalatal suture, which do not affect RME outcomes (40). The fact that these differences did not reach statistical significance in the inter-group comparison in our study, except for pre-peak patients, could be possibly due to an insufficient sample able to detect between group differences because the sample size calculations were focused to identify pre- and post-expansion changes; however, the results from the present RCT could be utilised for designing further research in this topic.

The design of the Keles expander was such that it was positioned much lower in the palate than either the Hyrax or Hybrid-Hyrax expander. This may explain why the oropharynx had a statistically significant change only in the Keles group which differs from published studies that found no changes in the oropharynx after rapid maxillary expansion (41). As the final CBCT scan was taken at appliance removal, the low position of the Keles expander may have trained the tongue to be in an altered position. It has been demonstrated that the tongue position can impact on orpharyngeal volumetric dimensions (42); however, long term follow-up would be required to assess if this altered tongue position is retained after removal of the appliance.

Controversy also exists with regards to the anteroposterior and vertical relationships of the craniofacial region and the airways. In dolichofacial and brachyfacial Class II children, the size of the upper airway did not differ statistically between facial types; however, the simulated with Computational Fluid Dynamics (CFDs) maximal pressure and velocity of the dolichofacial type were significantly higher to the brachyfacial type. Even though the depth and cross-sectional area of the airway did not exhibit morphologic differences, airway obstruction differed between different vertical phenotypes (43). The anteroposterior and vertical skeletal craniofacial morphology has not been significantly related with airway dimensions in Class Is, IIs and IIIs (44, 45); however, functional analyses showed significantly larger nasal resistance in Class II versus Class IIIs, correlated also with inferior tongue posture and decreased intermolar width (46). Other studies though showed greater airway volume in Class IIIs compared to Class Is and Class IIs (47) with the oropharyngeal airway being large and flat in Class IIIs as opposed to Class Is (48) and IIs (49). In the present study, anteroposterior and vertical craniofacial

characteristics did not have significant effects on the upper airway changes both in the whole sample and when testing for any differences between expanders.

As far as the reliability of the measurements is concerned, different scanning timings of the same patients resulted in different pharyngeal airway space values indicating the need for controlled and standardised patient positioning for reducing such inconsistencies; however, when the scans of the same time point were repeatedly measured by the same investigators, CBCT airway measurements showed high and adequate repeatability, which corroborates to our measurement error results (50). Significant methodological issues that could affect the reliability of airway measurements using CBCT are the lack of manual orientation of the images and selection of threshold sensitivity (51). Notwithstanding, the intra-examiner reliability improves with experience and is more consistent between examiners who are more educated and experienced in measuring the upper airways (52).

Dolphin's software automatic tool accuracy and reliability in airway analysis differed from manual segmentation by 9 to 43% meaning that the automatic tool is not accurate or reliable enough unless the scanning properties are conditioned, the measurements are standardized and the delineated airway is evaluated visually and uniformly by the observer (53). Threshold value standardisation or adjustment per individual case has been another parameter of debate. An ideal range of threshold values between 70 and 75 has been reported under laboratory conditions of an engineered homogenous prototype (27); however, this approach of applying strictly standardized threshold values does not take into account that tissues surrounding the upper airways may vary between patients with regards to their properties and subsequently the threshold values may need to be adjusted manually for each individual and not to rely on the softwares' automatic settings. No method or software comes without an expense, with automatic segmentation and thresholds leaving empty spaces within the rendered volumes while manual segmentation with operator controlled thresholds may overflow volume into another region (26). The threshold values in our study were manually adjusted and the range was 50-70. All scans were acquired by a specialist maxillofacial radiologist who followed the standardised protocol in patient positioning and instructions given to patients prior to scanning. In addition, the person performing the CBCT measurements developed a calibration through extensive experience, which was reflected in the agreement of repeated measurements.

Limitations

Like most longitudinal studies, there was attrition in each group, which was considerably higher in the Keles group due to technical failures of the appliance. This reduced number of patients in that group was less than the a priori calculated minimum sample of 15 patients/group needed to achieve sufficient power of the study. Subsequently, this may explain the lack of significant differences for the Keles appliances, which there might be there. The lack of statistically significant differences between devices in changing the airway volume between T0 and T1 indicates differences of small magnitude that might not be necessarily clinically relevant; however, a study with a larger sample size will be required to confirm these findings.

Additionally, it must be here stressed out that any benefits in term of increased airway volume obtained from RME are not necessarily translated in improved function for breathing-disordered patients. Neither adeno-tonsillectomy nor RME alone produce satisfying results, and only their combination leads to clinically relevant improvement in clinical and polysompographic outcomes (54). There are currently limited long-term data to justify the efficacy of dentofacial orthopaedics for paediatric sleep apnea (55), even though short-term evidence hints that RME might lead to improved quality of life of children with narrow maxilla and mild sleep apnea (56). All the above corroborate that there is currently insufficient robust data to support in an evidence-based manner the use of RME for the treatment of obstructive sleep apnea (57). Such recommendations can only be founded on sound clinically-relevant outcome such as improvements in morbidity rate, AHI, or the Eppworth Sleepiness Scale.

Although the accuracy of the CBCT in airway measurement is relatively well established (32), during the course of this research, a large degree of variation was seen in the sinus measurements possibly due to sinus inflammation with the most severe case demonstrated in Figure 5. This questions the validity of using CBCT to measure sinuses in patients with soft tissue inflammation; however, when we further analysed the total airways by excluding the values of the sinuses, results on total airways did not change for any group exclusion of the sinuses did not considerably impact the results. Additionally, random variation inherent to CBCT imaging of the upper airway, which can be due to operator errors in patient positioning within the tomograph and patient related parameters relevant to breathing or swallowing phases, was minimised by following a strictly controlled and standardized

protocol combined with detailed patient instructions for image acquisition (34, 50); however, it is not possible to fully be aware if the patients followed the given instructions.

The upper airway undergoes rapid growth during the first 3 years of life, then growth slows in rate and a second rapid growth phase occurs in adolescence (58). As our sample was within the adolescent growth spurt, the factor of growth cannot be fully ruled out; however, acquiring CBCTs from healthy, untreated controls within a 6 month interval cannot be justified for ethical reasons.

Finally, our patients have not been assessed by ENT specialists prior or after completion of the study for adenoids, tonsil size and any other kind of airway obstructions caused by mucosal and/or nasal conchae hypertrophy. As adenoid and tonsil sizes can be negatively correlated with the oropharyngeal airway in both Class IIs and Class IIIs (46) while nasal obstructions have been found to cause significant increases in maximum airflow velocity, inspiratory pressure drop and insipratory pressure loss coefficients in Continuous Positive Airway Pressure (CPAP) patients (59), it is obvious that the presence of such discrepancies would have an effect in the results. This could also be a possible explanation of the great inter-individual variability and range in the response to treatment as expressed in the great standard deviations, sometimes even 2 or 3 times above the mean difference seen in the total airway for the Hyrax and the Keles groups. For developing evidence-based recommendations, the European position paper on diagnostic tools in rhinology has reviewed and described several tools used to assess airway obstruction and concluded on the importance of prompt and accurate diagnosis for the appropriate management of sinonasal disease (60). Nevertheless, the readily available and traditional diagnostic approaches such as peak nasal inspiratory flow and acoustic rhinometry minimal cross-sectional area fail to meet the criteria of an ideal diagnostic test for breathing (61), which indicates a lack of consensus within medical specialities that have breathing assessment and upper respiratory organ function within their scope of practice.

The sample of the present study represents a random sample of an everyday clinical practice and thus it further substantiates that RME neither can be considered a sole and effective measure for increasing upper airway dimensions nor it can be simplistically related with improved breathing.

Generalizability

For any adolescent patient undergoing orthodontic treatment, growth is always a confounding factor impacting on results. As there were no controls in this trial, it was difficult to ascertain the impact that

growth may have on the airway volumetric change. Nonetheless, the randomization process which resulted in each patient having an equal chance of receiving any of the three devices resulted in a similar distribution of confounding variables in each group. As the treatment and assessment protocol were completed within a short time frame, the amount of growth as a confounding variable was also minimised. With the inclusion and exclusion criteria used in this trial, the patients treated in this study were similar to most orthodontic caseloads. Nonetheless, the patients of the present study were on average older to the ones usually receiving RME. This is due to the long public waitlists at the Sydney Dental Hospital. Theoretically though, the use of an older patient cohort could further demonstrate the effectiveness of the Hybrid-Hyrax expander in increasing the upper airway volume. Therefore, the short-term results of the present study are applicable to adolescent patients 10-16 years of age with maxillary transverse deficit.

Conclusion

All three RME appliances produce relatively small increases in the total volume of the upper airway (Hyrax: 3.8%, Hybrid-Hyrax: 8.3%, Keles expander: 4.5%), which casts doubts about their clinical relevance. No statistically significant differences were seen among the three appliances either for overall airway volume or for the volume of each specific airway compartment, with the sole exception of the nasopharynx. For all three expanders, greater changes were noted in patients with small baseline airway volumes. CVM stage had a significant impact on the effect of RME on airway volume, where pre-peak patients (CVM stages 1-3) experienced greater increases in total airway volume. Finally, among pre-peak patients, greater total airway increases were seen with Hybrid-Hyrax than with conventional Hyrax expanders.

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Figure legends

Figure 1. Expander design used in this study: Keles keyless expander (A), Hyrax expander (B), TAD placement prior to Hybrid-Hyrax insertion (C) and Hybrid-Hyrax expander (D).

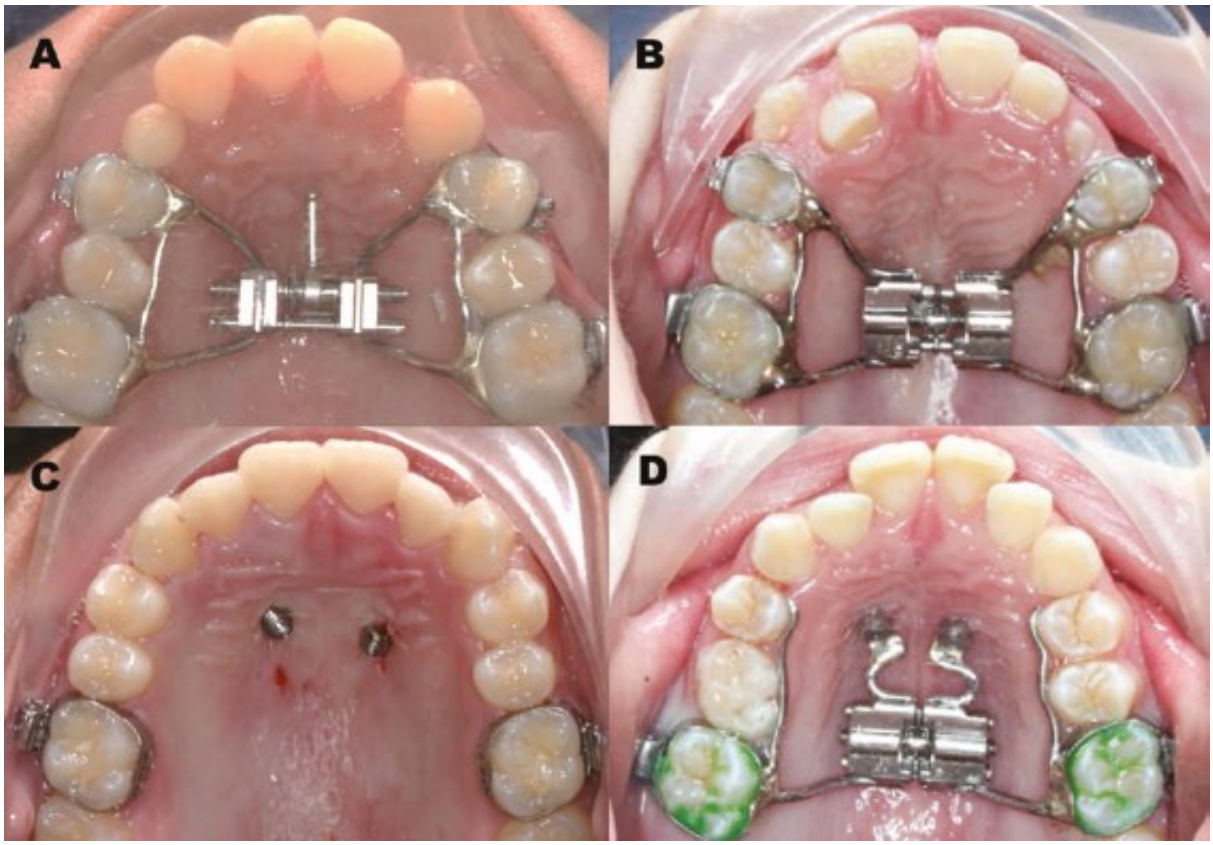

Figure 2. CBCT orientation prior to analysis. The sagittal plane was orientated in the Frankfort horizontal plane, with the coronal and axial plane orientated to the skeletal midline using the crista galli, anterior nasal spine, nasal bone and orbits as reference points.

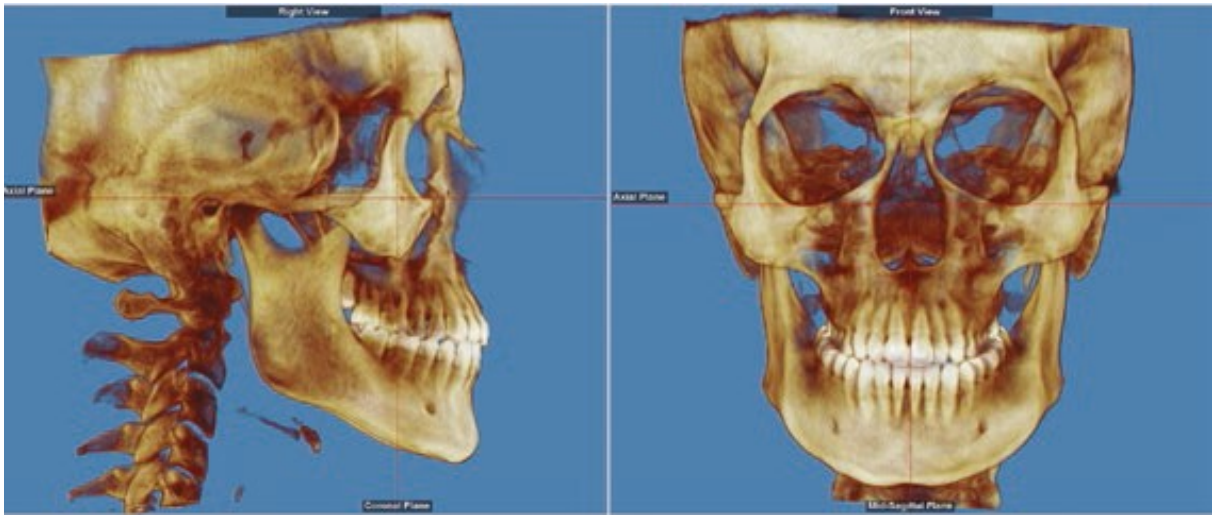

Figure 3. Boundaries used for the division of the airway taken in the sagittal section at the mid sagittal plane: Nasal cavity (A), Nasopharynx (B), Oropharynx (C) Hypopharynx (D). Boundaries used for the Sinus (E) taken at the coronal slice of the furcation of the first maxillary molar.

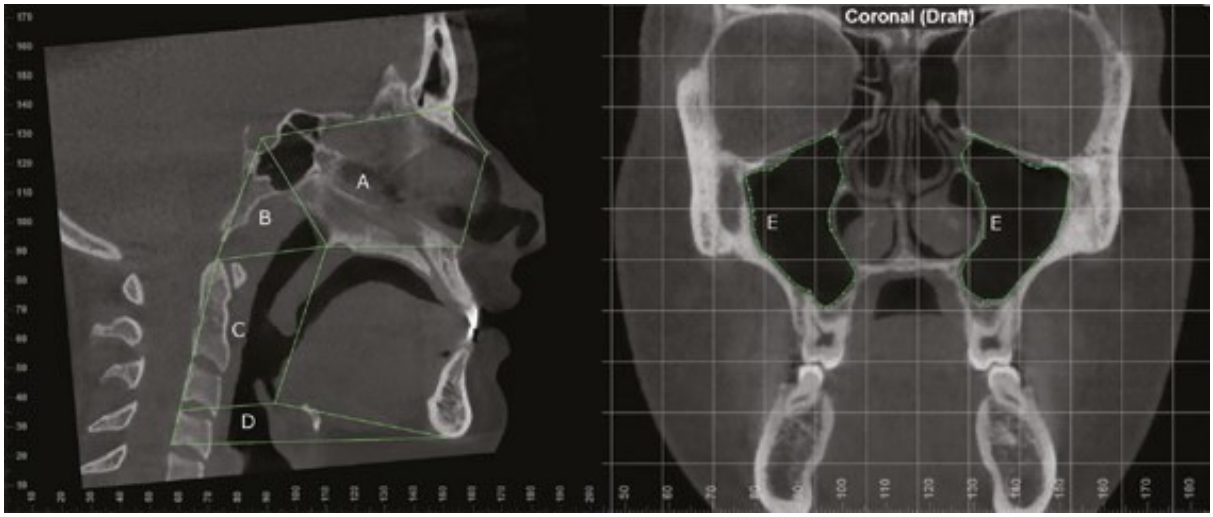

Figure 4. CONSORT patient flow diagram.

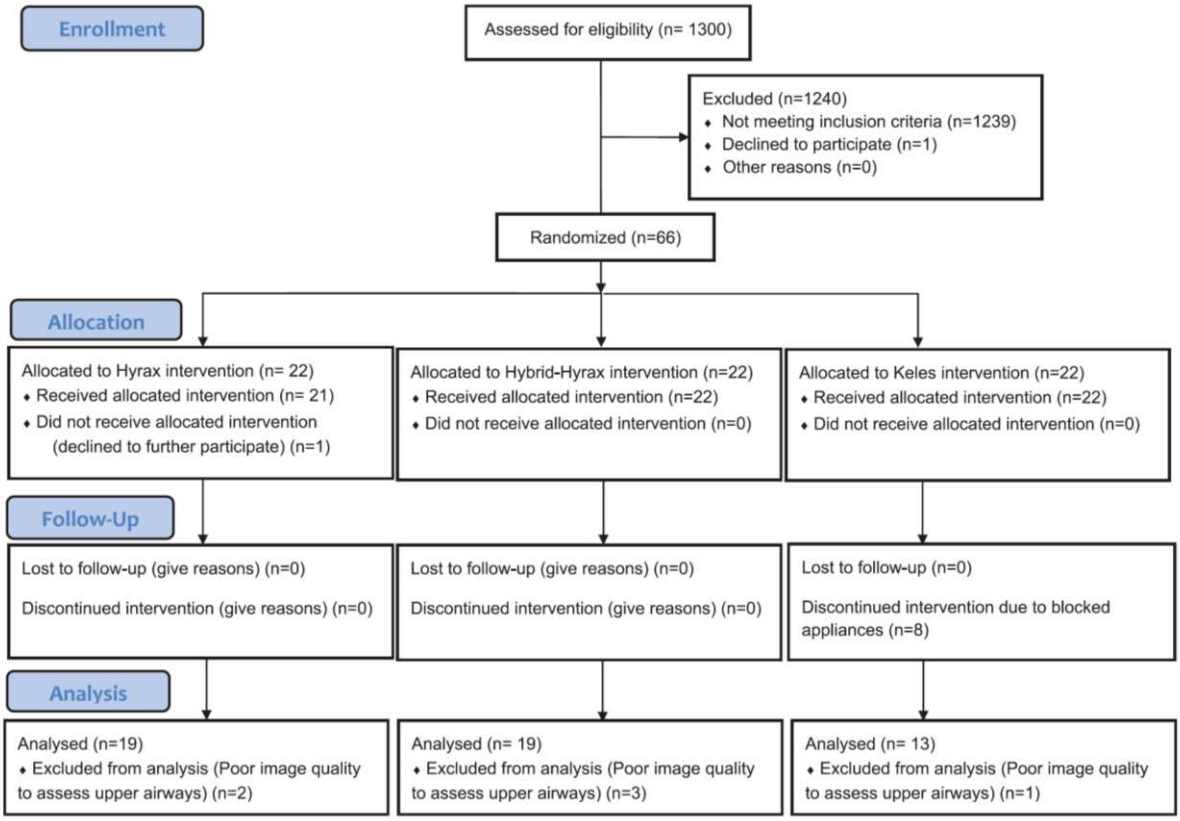

Figure 5. Three dimensional (3D) representations of the sinuses of the same patient at T0 (A) and T1 (B). The marked differences in the sinus volume of the left sinus are notable and could be attributed to possible inflammation.

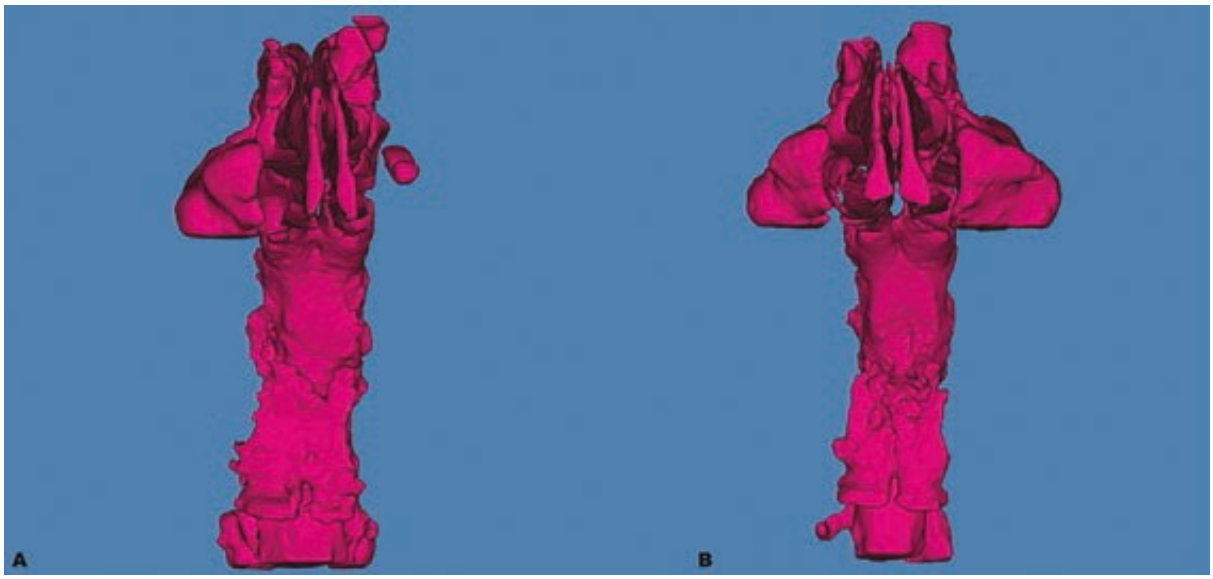

Table 1. Definition of the anatomic upper airway compartments in the sagittal view.

	Anterior boundary	Posterior boundary	Superior boundary	Inferior boundary
Nasal cavity	Line from Anterior Nasal Spine (ANS) to the tip of the nasal bone to Nasion (Na)	Line from Sella (S) to the Posterior Nasal Spine (PNS)	Line from Nasion (N) to Sella (S)	Line from Anterior Nasal Spine (ANS) to the Posterior Nasal Spine (PNS)
Nasopharynx	Line from Sella (S) to the Posterior Nasal Spine (PNS)	Line from Sella (S) to the tip of the odontoid process		Line from Posterior nasal Spine (PNS) to the tip of the odontoid process
Oropharynx	Line from Posterior Nasal Spine (PNS) to the epiglottis	Line from the tip of the odontoid process to the posterior-superior border of the 4th cervical vertebra (CV4)	Line extending from the Posterior Nasal Spine (PNS) to the tip of the odontoid process	Line from the base of the epiglottis to the posterior-superior border of the 4th cervical vertebra (CV4)
Hypopharynx	Line extending from the base of the epiglottis to the inferior border of the symphysis	Line extending from the posterior-superior corner of the 4th cervical vertebra (CV4) to the posterior-inferior corner of the 4th cervical vertebra (CV4)	Line extending from the base of the epiglottis to the posterior-superior corner of the 4th cervical vertebra (CV4)	Line extending from the posterior-inferior corner of the 4th cervical vertebra (CV4) to the inferior border of the symphysis

Table 2. Characteristics of the included patients.

Factor	Category	Hyrax (n=19)	Hybrid (n=19)	Keles (n=13)	P
Age (years)	Mean (SD)	13.8 (1.6)	14.3 (1.7)	14.6 (1.2)	0.41*
Gender	Male – n (%)	10 (53%)	8 (42%)	2 (15%)	0.09†
	Female – n (%)	9 (47%)	11 (58%)	11 (85%)	
CVM stage	2 – n (%)	1 (5%)	0 (0%)	0 (0%)	0.28†
	3 – n (%)	4 (21%)	4 (21%)	0 (0%)	
	4 – n (%)	6 (32%)	8 (42%)	6 (46%)	
	5 – n (%)	6 (32%)	4 (21%)	7 (54%)	
	6 – n (%)	2 (11%)	3 (16%)	0 (0%)	
CVM stage category	Pre-peak (1-3)	5 (26%)	4 (21%)	0 (0%)	0.14†
	Mid- or post-peak (4-6)	14 (74%)	15 (79%)	13 (100%)	
Expansion width (mm)	Mean (SD)	9.1 (2.6)	9.1 (2.2)	6.2 (2.7)	0.002*
SNA (°)	Mean (SD)	77.9 (3.5)	79.6 (4.6)	79.8 (3.4)	0.31*
SNB (°)	Mean (SD)	76.0 (4.5)	77.9 (5.1)	78.3 (2.5)	0.28*
ANB (°)	Mean (SD)	1.9 (2.9)	1.7 (2.7)	1.5 (2.7)	0.93*
Wits (mm)	Mean (SD)	-1.5 (4.2)	-1.4 (4.4)	-1.2 (4.2)	0.99*
SN-ML (°)	Mean (SD)	36.9 (7.2)	34.8 (6.9)	33.8 (4.6)	0.42*
NA-APog	Mean (SD)	2.3 (7.1)	1.4 (6.5)	0.4 (5.4)	0.73*
SN (mm)	Mean (SD)	64.8 (3.0)	66.1 (4.0)	64.9 (2.9)	0.45*
Co-A (mm)	Mean (SD)	79.0 (5.9)	79.2 (5.5)	78.8 (3.8)	0.99*
Co-Gn (mm)	Mean (SD)	107.3 (9.1)	108.8 (6.7)	109.5 (3.9)	0.67*

CVM, cervical vertebrae maturation method; n, number of patients; SD, standard deviation.

* from one-way analysis of variance

† From Fisher's exact test CVM, cervical vertebrae maturation method; SD, standard deviation.

Table 3. Airway measurements and differences between before (T0) and after (T1) treatment in the three groups.

Outcome	**Group**	**T0 – mean (SD)**	**T1 – mean (SD)**	**ΔT1-T0 – mean (SD)**	**ΔT1-T0 (%)**	P*
Sinus	Hyrax (n=19)	23433.05 (9577.7)	23813.4 (8131.1)	380.4 (2973.4)	+1.6%	0.13
	Hybrid-Hyrax (n=19)	24138.8 (7862.1)	25346.3 (8558.9)	1207.5 (1944.8)	+5.0%	
	Keles (n=13)	24184.6 (8578.8)	26470.2 (7734.1)	2285.5 (3608.9)	+9.5%	
Nasal cavity	Hyrax (n=19)	25298.2 (9403.8)	26364.3 (8645.1)	1066.1 (8793.0)	+4.2%	0.32
	Hybrid-Hyrax (n=19)	26630.8 (5659.0)	29319.5 (5536.7)	2688.7 (3377.0)	+10.1%	
	Keles (n=13)	23449.2 (7856.0)	24725.6 (6472.9)	1276.4 (5554.6)	+5.4%	
Nasopharynx	Hyrax (n=19)	4663.5 (2691.4)	4637.4 (2725.5)	-26.1 (1403.0)	-0.6%	0.04
	Hybrid-Hyrax (n=19)	5416.8 (2194.0)	6362.4 (2443.8)	945.6 (953.6)	+17.5%	
	Keles (n=13)	5585.2 (3073.1)	6764.5 (3240.8)	1179.4 (2253.2)	+21.1%	
Oropharynx	Hyrax (n=19)	9465.6 (2757.6)	10788.7 (4047.3)	1323.1 (2853.6)	+14.0%	0.89
	Hybrid-Hyrax (n=19)	11651.8 (6208.3)	12702.7 (5678.1)	1050.8 (2780.0)	+9.0%	
	Keles (n=13)	10517.4 (3537.2)	12060.5 (1973.9)	1543.2 (2480.1)	+14.7%	
Hypopharynx	Hyrax (n=19)	3494.6 (1052.4)	3289.1 (1201.2)	-205.5 (1008.5)	-5.9%	0.45
	Hybrid-Hyrax (n=19)	3441.9 (1430.0)	3451.3 (1290.9)	9.4 (756.5)	+0.3%	
	Keles (n=13)	3273.1 (1301.7)	2924.5 (1112.6)	-348.5 (1351.2)	-10.6%	
Total airway	Hyrax (n=19)	66355.0 (19540.8)	68892.9 (18038.0)	2537.9 (6603.7)	+3.8%	0.19
	Hybrid-Hyrax (n=19)	71280.2 (15359.3)	77182.2 (14684.1)	5902.1 (5992.9)	+8.3%	
	Keles (n=13)	67009.5 (16069.5)	70020.9 (15349.2)	3001.4 (10909.9)	+4.5%	
Total excluded sinuses	Hyrax (n=19)	42921.9 (12744.1)	45079.5 (12087.1)	2157.6 (8444.9)	+5.0%	0.26
	Hybrid-Hyrax (n=19)	47141.4 (11544.2)	51835.9 (10598.0)	4694.5 (5087.3)	+10.0%	
	Keles (n=13)	42824.9 (11054.4)	46475.2 (9539.3)	3650.4 (8726.9)	+8.5%	

SD, standard deviation.

* Wald linear regression for the effect of expansion group on the T1 value, with T0 value as covariate.

Supplementary Table 1. Explorative linear regression analyses on confounders for the change in total upper airway T1-T0 across the whole sample (all three expansion groups).

Factor	Category	b (95% CI)	P
Gender	Female	Reference	
	Male	-2656.4 (-7087.0, 1774.2)	0.23
Age	Per year	-952.0 (-2322.9, 418.9)	0.17
CVM	Stage 2	Reference	0.59
	Stage 3	4314.3 (-12367.8, 20996.3)	
	Stage 4	2684.1 (-13432.3, 18800.4)	
	Stage 5	-432.9 (-16616.8, 15751.1)	
	Stage 6	3803.6 (-13425.5, 21032.7)	
CVM stage	Pre-peak (CVM 1-3)	Reference	
	Mid- or post-peak (CVM 4-6)	-2279.2 (-7999.7, 3441.3)	0.43
Expansion width	Per mm	-370.4 (-1168.0, 427.2)	0.36
Total airway at T0	Per mm^3	-0.1 (-0.3, 0)	0.02
SNA	Per °	396.2 (-162.6, 954.9)	0.16
SNB	Per °	345.4 (-157.5, 848.4)	0.17
ANB	Per °	-80.7 (-912.3, 750.9)	0.85
Wits	Per mm	-356.3 (-885.5, 172.9)	0.18
SN-MP	Per °	34.6 (-310.1, 379.2)	0.84
Convexity	Per °	41.4 (-311.0, 393.7)	0.81
SN	Per mm	-87.7 (-754.7, 579.2)	0.79
Co-A	Per mm	-27.9 (-463.2, 407.3)	0.90
Co-Gn	Per mm	20.5 (-297.9, 339.0)	0.90

b, unstandardized regression coefficient; CI, confidence interval; CVM, cervical vertebrae maturation method. * overall omnibus test across all CVM stages.

Supplementary Table 2. Adjusted linear regressions on total airway after (T1) treatment accounting for potential confounders.

Factor	Category	b (95% CI)	P	Interaction with expander group†
Expander	Hyrax	Reference	0.19*	
	Hybrid-Hyrax	4145.8 (-654.5, 8946.0)		
	Keles	577.3 (-4706.1, 5860.7)		
Airway T0	Per mm^3	0.8 (0.7, 1.0)	<0.001	Not tested
Expander	Hyrax	Not tested		
	Hybrid-Hyrax	Not tested		
	Keles	Not tested		
Airway T0	Per mm^3	Not tested		
Age	Per year	Not tested		0.004
Expander	Hyrax	Reference	0.18*	
	Hybrid-Hyrax	3863.5 (-963.4, 8690.5)		
	Keles	-296.3 (-5831.7, 5239.1)		
Airway T0	Per mm^3	0.8 (0.7, 1.0)	<0.001	
Sex	Female	Reference		
	Male	-2332.4 (-6771.8, 2106.9)	0.30	0.93
Expander	Hyrax	Not tested		
	Hybrid-Hyrax	Not tested		
	Keles	Not tested		
Airway T0	Per mm^3	Not tested		
CVM stage	Pre-peak	Not tested		0.04
	Mid- or post-peak	Not tested		
Expander	Hyrax	Reference	0.13*	
	Hybrid-Hyrax	4193.3 (-589.4, 8976.0)		
	Keles	-909.0 (-6742.8, 4924.9)		
Airway T0	Per mm^3	0.9 (0.7, 1.0)	<0.001	
Expansion	Per mm	-543.8 (-1464.5, 376.9)	0.24	0.13
Expander	Hyrax	Reference	0.21*	
	Hybrid-Hyrax	4102.0 (-887.6, 9091.5)		
	Keles	525.3 (-4940.3, 5991.0)		
Airway T0	Per mm^3	0.9 (0.7, 1.0)	<0.001	
SNA	Per degree	238.1 (-316.9, 793.1)	0.39	0.69
Expander	Hyrax	Reference	0.21*	
	Hybrid-Hyrax	3974.2 (-954.3, 8902.7)		
	Keles	309.8 (-5117.8, 5737.3)		
Airway T0	Per mm^3	0.8 (0.7, 1.0)	<0.001	
SNB	Per degree	299.5 (-189.3, 788.3)	0.22	0.53
Expander	Hyrax	Reference	0.16*	
	Hybrid-Hyrax	4536.8 (-350.3, 9423.8)		
	Keles	877.8 (-4497.4, 6253.0)		
Airway T0	Per mm^3	0.8 (0.7, 1.0)	<0.001	
ANB	Per degree	-307.6 (-1109.0, 493.8)	0.44	0.44
Expander	Hyrax	Reference	0.16*	
	Hybrid-Hyrax	4527.3 (-318.5, 9373.1)		
	Keles	1055.5 (-4268.3, 6379.3)		
Airway T0	Per mm^3	0.8 (0.7, 1.0)	<0.001	
Wits	Per mm	-293.6 (-797.3, 210.1)	0.25	0.30

Expander	Hyrax	Reference	0.17*	
	Hybrid-Hyrax	4515.7 (-434.7, 9466.1)		
	Keles	924.5 (-4570.7, 6419.8)		
Airway T0	Per mm^3	0.8 (0.7, 1.0)	<0.001	
SN-ML	Per degree	-20.6 (-358.1, 316.9)	0.90	0.06
Expander	Hyrax	Reference	0.16*	
	Hybrid-Hyrax	4519.4 (-387.6, 9426.4)		
	Keles	828.1 (-4596.9, 6253.1)		
Airway T0	Per mm^3	0.8 (0.7, 1.0)	<0.001	
Convexity	Per degree	-87.8 (-438.5, 263.0)	0.62	0.55
Expander	Hyrax	Reference	0.19*	
	Hybrid-Hyrax	4344.6 (-588.3		
	Keles	977.1 (-4399.2, 6353.4)		
Airway T0	Per mm^3	0.8 (0.7, 1.0)	<0.001	
SN	Per mm	240.6 (-477.7, 958.9)	0.50	0.95
Expander	Hyrax	Reference	0.14*	
	Hybrid-Hyrax	4703.9 (-136.9, 9544.7)		
	Keles	1046.9 (-4264.3, 6358.0)		
Airway T0	Per mm^3	0.8 (0.7, 0.9)	<0.001	
Co-A	Per mm	290.1 (-173.1, 753.2)	0.21	0.30
Expander	Hyrax	Reference	0.14*	
	Hybrid-Hyrax	4413.3 (-354.2, 9180.8)		
	Keles	363.0 (-4921.1, 5647.2)		
Airway T0	Per mm^3	0.8 (0.6, 0.9)	<0.001	
Co-Gn	Per mm	297.8 (-50.5, 646.2)	0.09	0.83

CI, confidence interval; CVM, cervical vertebral maturation.
* from Wald test for overall differences between any of the three expansion groups.
† tested initially in a model with expander group and baseline airway, but then dropped from the model, unless statistically significant. Then a stratified model was constructed.

Supplementary Table 3. Adjusted linear regressions on total airway after (T1) treatment accounting for potential confounders.

		Pre-peak (CVM 1-3)			Mid- or post-peak group (CVM 4-6)	
Factor	**Category**	**b (95% CI)**	**P**		**b (95% CI)**	**P**
Expander	Hyrax	Reference			Reference	0.73
	Hybrid-Hyrax	12110 (3297.8, 20922.4)	0.02		1592.8 (-4033.3, 7219.0)	
	Keles	-	-		-568.8 (-6404.8, 5267.2)	
Airway T0	Per mm^3	0.9 (0.6, 1.2)	<0.001		0.8 (0.7, 1.0)	<0.001

CI, confidence interval; CVM, cervical vertebral maturation.
* from Wald test for overall differences between any of the three expansion groups.